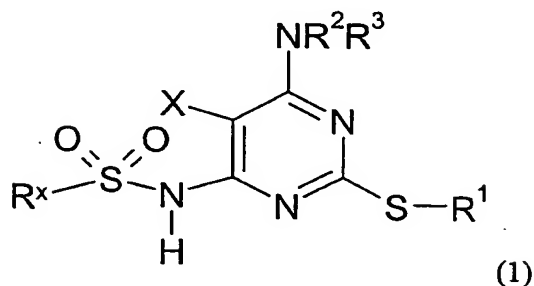


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CLAIMS

1. A compound of formula (1), pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof:

5



wherein R<sup>1</sup> is a group selected from C<sub>3-7</sub>carbocyclyl, C<sub>1-8</sub>alkyl, C<sub>2-6</sub>alkenyl and C<sub>2-6</sub>alkynyl;  
 10 wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from fluoro, nitrile, -OR<sup>4</sup>, -NR<sup>5</sup>R<sup>6</sup>, -CONR<sup>5</sup>R<sup>6</sup>, -COOR<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -SR<sup>10</sup>, -SO<sub>2</sub>R<sup>10</sup>, -SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup>, phenyl or heteroaryl; wherein phenyl and heteroaryl are optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, -OR<sup>4</sup>, -NR<sup>5</sup>R<sup>6</sup>, -CONR<sup>5</sup>R<sup>6</sup>, -COOR<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -SR<sup>10</sup>, -SO<sub>2</sub>R<sup>10</sup>, -SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup>,  
 15 C<sub>1-6</sub>alkyl and trifluoromethyl;

wherein R<sup>2</sup> is C<sub>3-7</sub>carbocyclyl, optionally substituted by 1, 2 or 3 substituents independently selected from:

- (a) fluoro, -OR<sup>4</sup>, -NR<sup>5</sup>R<sup>6</sup>, -CONR<sup>5</sup>R<sup>6</sup>, -COOR<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -SR<sup>10</sup>, -SO<sub>2</sub>R<sup>10</sup>, -SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>,  
 20 -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup>;  
 (b) a 3-8 membered ring optionally containing 1, 2 or 3 atoms selected from O, S, -NR<sup>8</sup> and whereby the ring is optionally substituted by C<sub>1-3</sub>alkyl or fluoro; or  
 (c) phenyl or heteroaryl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, -OR<sup>4</sup>, -NR<sup>5</sup>R<sup>6</sup>, -CONR<sup>5</sup>R<sup>6</sup>, -NR<sup>8</sup>COR<sup>9</sup>, -  
 25 SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup>, C<sub>1-6</sub>alkyl and trifluoromethyl;

or R<sup>2</sup> is a group selected from C<sub>1-8</sub>alkyl, C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkynyl wherein the group is substituted by 1, 2 or 3 substituents independently selected from hydroxy, amino, C<sub>1-6</sub>alkoxy,

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C<sub>1-6</sub>alkylamino, di(C<sub>1-6</sub>alkyl)amino, *N*-(C<sub>1-6</sub>alkyl)-*N*-(phenyl)amino, *N*-C<sub>1-6</sub>alkylcarbamoyl, *N,N*-di(C<sub>1-6</sub>alkyl)carbamoyl, *N*-(C<sub>1-6</sub>alkyl)-*N*-(phenyl)carbamoyl, carboxy, phenoxycarbonyl, -NR<sup>8</sup>COR<sup>9</sup>, -SO<sub>2</sub>R<sup>10</sup>, -SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup> and -NR<sup>8</sup>SO<sub>2</sub>R<sup>9</sup>;

5 wherein R<sup>3</sup> is hydrogen or independently R<sup>2</sup>;

R<sup>4</sup> is hydrogen or a group selected from C<sub>1-6</sub>alkyl and phenyl, wherein the group is optionally substituted by 1 or 2 substituents independently selected from halo, phenyl, -OR<sup>11</sup> and -NR<sup>12</sup>R<sup>13</sup>;

10

R<sup>5</sup> and R<sup>6</sup> are independently hydrogen or a group selected from C<sub>1-6</sub>alkyl and phenyl wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, phenyl, -OR<sup>14</sup>, -NR<sup>15</sup>R<sup>16</sup>, -COOR<sup>14</sup>, -CONR<sup>15</sup>R<sup>16</sup>, -NR<sup>15</sup>COR<sup>16</sup>, -SO<sub>2</sub>R<sup>10</sup>, -SONR<sup>15</sup>R<sup>16</sup> and NR<sup>15</sup>SO<sub>2</sub>R<sup>16</sup>

15 or

R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally containing a further heteroatom selected from oxygen and nitrogen atoms, which ring is optionally substituted by 1, 2 or 3 substituents independently selected from phenyl, -OR<sup>14</sup>, -COOR<sup>14</sup>, -NR<sup>15</sup>R<sup>16</sup>, -CONR<sup>15</sup>R<sup>16</sup>,  
20 -NR<sup>15</sup>COR<sup>16</sup>, -SO<sub>2</sub>R<sup>10</sup>, -SONR<sup>15</sup>R<sup>16</sup>, NR<sup>15</sup>SO<sub>2</sub>R<sup>16</sup> or C<sub>1-6</sub>alkyl (optionally substituted by 1 or 2 substituents independently selected from halo, -NR<sup>15</sup>R<sup>16</sup> and -OR<sup>17</sup> groups);

R<sup>10</sup> is hydrogen or a group selected from C<sub>1-6</sub>alkyl or phenyl, wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, phenyl, -OR<sup>17</sup> and -  
25 NR<sup>15</sup>R<sup>16</sup>; and

each of R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> is independently hydrogen, C<sub>1-6</sub>alkyl or phenyl;

30 X is hydrogen, halo, cyano, nitro, hydroxy, C<sub>1-6</sub>alkoxy (optionally substituted by 1 or 2 substituents selected from halo, -OR<sup>11</sup> and -NR<sup>12</sup>R<sup>13</sup>), -NR<sup>5</sup>R<sup>6</sup>, -COOR<sup>7</sup>, -NR<sup>8</sup>COR<sup>9</sup>, thio, C<sub>1-6</sub>alkylthio (optionally substituted by 1 or 2 substituents selected from halo, -OR<sup>17</sup>, -NR<sup>15</sup>R<sup>16</sup>), -SO<sub>2</sub>R<sup>10</sup> or a group selected from C<sub>3-7</sub>carbocyclyl, C<sub>1-8</sub>alkyl, C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkynyl,

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wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo,  $-OR^4$ ,  $-NR^5R^6$ ,  $-CONR^5R^6$ ,  $-COOR^7$ ,  $-NR^8COR^9$ ,  $-SR^{10}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^5R^6$  and  $-NR^8SO_2R^9$ ;

- 5  $R^x$  is trifluoromethyl,  $-NR^5R^6$ , phenyl, naphthyl, monocyclic or bicyclic heteroaryl wherein a heteroring may be partially or fully saturated and one or more ring carbon atoms may form a carbonyl group, and wherein each phenyl or heteroaryl group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro,  $-OR^4$ ,  $-NR^5R^6$ ,  $-CONR^5R^6$ ,  $-COR^7$ ,  $-COOR^7$ ,  $-NR^8COR^9$ ,  $-SR^{10}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^5R^6$ ,  $-NR^8SO_2R^9$ ,  $C_{1-6}$ alkyl or
- 10 trifluoromethyl;  
or  $R^x$  is a group selected from  $C_{3-7}$ carbocyclyl,  $C_{1-8}$ alkyl,  $C_{2-6}$ alkenyl and  $C_{2-6}$ alkynyl whereby the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo,  $-OR^4$ ,  $-NR^5R^6$ ,  $-CONR^5R^6$ ,  $-COR^7$ ,  $-COOR^7$ ,  $-NR^8COR^9$ ,  $-SR^{10}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^5R^6$ ,  $-NR^8SO_2R^9$ , phenyl or heteroaryl; and wherein each phenyl or heteroaryl group is optionally
- 15 substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro,  $-OR^4$ ,  $-NR^5R^6$ ,  $-CONR^5R^6$ ,  $-COR^7$ ,  $-COOR^7$ ,  $-NR^8COR^9$ ,  $-SR^{10}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^5R^6$ ,  $-NR^8SO_2R^9$ ,  $C_{1-6}$ alkyl or trifluoromethyl;  
or  $R^x$  and X together form a 4 to 8-membered sulfonamide ring optionally substituted by 1, 2 or 3 substituents independently selected from halo,  $-OR^4$ ,  $-NR^5R^6$ ,  $-CONR^5R^6$ ,  $-COOR^7$ ,  $-NR^8COR^9$ ,  $-SR^{10}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^5R^6$ ,  $-NR^8SO_2R^9$ , phenyl or heteroaryl; wherein phenyl and heteroaryl are optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro,  $-OR^4$ ,  $-NR^5R^6$ ,  $-CONR^5R^6$ ,  $-COOR^7$ ,  $-NR^8COR^9$ ,  $-SR^{10}$ ,  $-SO_2R^{10}$ ,  $-SO_2NR^5R^6$ ,  $-NR^8SO_2R^9$ ,  $C_{1-6}$ alkyl and trifluoromethyl.
- 20
- 25 2. A compound, pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof according to claim 1 wherein  $R^2$  is  $C_{1-8}$ alkyl optionally substituted by 1 or 2 hydroxy substituents.
3. A compound, pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester
- 30 thereof according to claim 1 wherein  $R^1$  is benzyl optionally substituted by 1, 2 or 3 substituents independently selected from fluoro, chloro, bromo, methoxy, methyl and trifluoromethyl.

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4. A compound, pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof wherein R<sup>3</sup> is hydrogen;
5. A compound, pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof wherein X is hydrogen
6. A compound, pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof wherein R<sup>x</sup> is methyl, 1-methylimidazolyl, 1,2-dimethylimidazolyl, *N,N*-dimethylamino, azetidiny, pyrrolidiny, morpholinyl and piperidiny.
- 10 7. A compound selected from the group consisting of:  
*N*-(2-[(3-Chloro-2-fluorobenzyl)thio]-6-[[*(1R)*-2-hydroxy-1-methylethyl]amino]-pyrimidin-4-yl)methanesulfonamide  
*N*-[2-[(3-Chloro-2-fluorobenzyl)thio]-6-[(2-hydroxy-1-methylethyl)amino]-4-pyrimidinyl]-4-morpholinesulfonamide  
*N*-[2-[(3-Chloro-2-fluorophenyl)methyl]thio]-6-[(2-hydroxy-1-methylethyl)amino]-4-pyrimidinyl]-1,2-dimethyl-1*H*-imidazole-4-sulfonamide  
*N*-(2-[(2,3-Difluorobenzyl)thio]-6-[[*(1R)*-2-hydroxy-1-methylethyl]amino]pyrimidin-4-yl)piperidine-1-sulfonamide  
20 *N*-(2-[(2,3-Difluorobenzyl)thio]-6-[[*(1R)*-2-hydroxy-1-methylethyl]amino]pyrimidin-4-yl)pyrrolidine-1-sulfonamide  
*N*-(2-[(2,3-Difluorobenzyl)thio]-6-[[*(1R)*-2-hydroxy-1-methylethyl]amino]pyrimidin-4-yl)azetidine-1-sulfonamide  
*N*-{6-[[*(1R)*-2-Hydroxy-1-methylethyl]amino]-2-[(2,3,4-trifluorobenzyl)thio]-pyrimidin-4-yl}morpholine-4-sulfonamide  
25 *N*-(2-[(2,3-Difluorobenzyl)thio]-6-[[*(1R)*-2-hydroxy-1-methylethyl]amino]pyrimidin-4-yl)morpholine-4-sulfonamide  
*N*-(2-[(3-Chloro-2-fluorobenzyl)thio]-6-[[*(1R)*-2-hydroxy-1-methylethyl]amino]-pyrimidin-4-yl)azetidine-1-sulfonamide  
30 *N*-{6-[[*(1R)*-2-Hydroxy-1-methylethyl]amino]-2-[(2,3,4-trifluorobenzyl)thio]-pyrimidin-4-yl}azetidine-1-sulfonamide  
*N'*-(2-[(3-Chloro-2-fluorobenzyl)thio]-6-[[*(1R)*-2-hydroxy-1-methylethyl]amino]-pyrimidin-4-yl)-*N,N*-dimethylsulfamide

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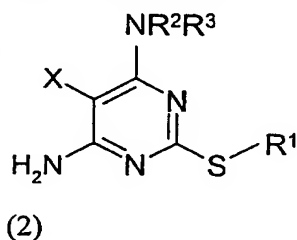
*N*-[2-[[[(3-Chloro-2-fluorophenyl)methyl]thio]-6-[(*R*)-(2-hydroxy-1-methylethyl)amino]-4-pyrimidinyl]-1-methyl-1*H*-imidazole-4-sulfonamide;

and a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof.

- 5 8. A compound, pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof according to any one of claims 1 to 7 for use as a medicament.
9. A compound, pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof according to any one of claims 1 to 7 for use as a medicament for the treatment of
- 10 asthma, allergic rhinitis, COPD, inflammatory bowel disease, osteoarthritis, osteoporosis, rheumatoid arthritis, or psoriasis..
10. A compound, pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof according to any one of claims 1-7, for use as a medicament for the treatment of
- 15 cancer.
11. The use of a compound, pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, according to any one of claims 1 to 7 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of
- 20 chemokine receptor activity is beneficial.
12. The use of a compound, pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, according to any one of claims 1 to 7 in the manufacture of a medicament for the treatment of asthma, allergic rhinitis, COPD, inflammatory bowel
- 25 disease, irritable bowel syndrome, osteoarthritis, osteoporosis, rheumatoid arthritis, or psoriasis.
13. The use of a compound, pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, according to any one of claims 1 to 7 in the manufacture of a
- 30 medicament for the treatment of cancer.

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14. A pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof according to any one of claims 1 to 7; and a pharmaceutically-acceptable diluent or carrier.
- 5 15. A process for the preparation of a compound according to claim 1 comprising the steps of:
- a) treating a compound of formula (2):

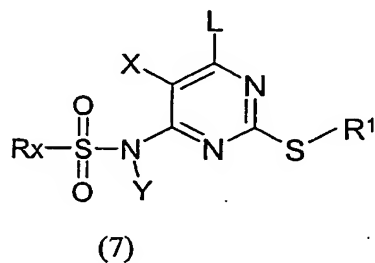


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wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $X$  are as defined in claim 1, with sulfonyl chlorides ( $R^xSO_2Cl$  where  $R^x$  is as defined in claim 1;

or

- b) treating a compound of formula (7):



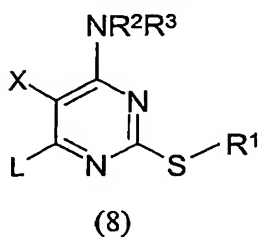
15

wherein  $R^1$ ,  $R^x$  and  $X$  are as defined in formula (1),  $L$  is a halogen and  $Y$  is either hydrogen or a protecting group with nucleophilic amines of the type  $NR^2R^3$  as defined in formula (1) in

- 20 the presence or absence of a suitable base and solvent;

or

- c) treating a compound of formula (8):



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wherein  $R^1$ ,  $R^x$  and X are as defined in formula (1) and L is halogen, with sulfonamides of formula  $R^xSO_2NH_2$  where  $R^x$  is as defined in formula (1) except  $NR^5R^6$  in the presence of a suitable base and solvent.

and

- 5 independently for each of process variants a), b) or c), optionally thereafter (i), (ii), (iii), (iv) or (v) in any order:
  - i) removing any protecting groups;
  - ii) converting the compound of formula (1) into a further compound of formula (1)
  - iii) forming a salt
  - 10 iv) forming a prodrug
  - v) forming an *in vivo* hydrolysable ester.
16. A combination therapy which comprises administering a compound of formula (1) or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, or a
- 15 pharmaceutical composition or formulation comprising a compound of formula (1), concurrently or sequentially with other therapy and/or another pharmaceutical agent.
17. A combination therapy as claimed in claim 16 for the treatment of asthma, allergic rhinitis, COPD, inflammatory bowel disease, irritable bowel syndrome, osteoarthritis,
- 20 osteoporosis, rheumatoid arthritis, or psoriasis.
18. A combination therapy as claimed in claim 16 for the treatment of cancer.
19. A pharmaceutical composition which comprises a compound of formula (1) or a
- 25 pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, in conjunction with another pharmaceutical agent.
20. A pharmaceutical composition as claimed in claim 19 for the treatment of asthma, allergic rhinitis, COPD, inflammatory bowel disease, irritable bowel syndrome, osteoarthritis,
- 30 osteoporosis, rheumatoid arthritis, or psoriasis.
21. A pharmaceutical composition as claimed in claim 19 for the treatment of cancer.